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Synthesis and anti-tumor activities of new [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives

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ABSTRACT

Condensation of 1*H*-1,2,4-triazol-5-amine with the appropriate sodium (*E*)-(2-oxocycloalkylidene)methanolate gave 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4]triazolo [1,5-*a*]pyrimidine, 6,7,8,9-tetrahydro-[1,2,4]triazolo[1,5-*a*]quinazoline, 7,8,9,10-tetra hydro-6*H*-cyclohepta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine and 6,7,8,9,10,11-hexahydro cycloocta [*e*][1,2,4]triazolo[1,5-*a*]pyrimidine. Structures of the newly synthesized compounds were elucidated via elemental analyses, spectral (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR), and X-ray single crystal diffraction data. These derivatives showed potent anti-tumor cytotoxic activity in vitro using different human cancer cell lines.

1. Introduction

Triazolopyrimidines represent a pharmaceutically important class of compounds because of their diverse range of biological activities, such as antitumor [1], cytotoxicity [2], therapeutic potentiality [3], potent and selective ATP site directed inhibition of the EGF-receptor protein tyrosine kinase [4] and cardiovascular [5] activities. In addition, they have been found in DNA-interactive drugs [6] and as useful building blocks in the synthesis of herbicidal drugs, e.g. *Metosulam*, *Flumetsulam*, *Azafenidin, Diclosulam*, *Penoxsulam*, *Floransulan*, *Cloransulam* etc. Also, various derivatives of 1,2,4-triazolo[4,3-*a*]pyrimidine were reported to be useful as calcium-channel-blocking vasodilators, some have antihypertensive [7], cardiovascular [8,9] and anxiolytic [10] activities.

In view of these reports and in continuation of our interest in the synthesis of a variety of heterocyclic systems for biological evaluation [11-17], we describe herein a facile synthesis of some new 1,2,4-triazolo[5,1-*a*]pyrimidine derivatives and study the anti-carcinogenic effects of two newly synthesized derivatives, 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4] triazolo[1,5-*a*]pyrimidine and 6,7,8,9,10,11-hexahydrocyclo octa[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine against human hepato-carcinoma (HepG2) and breast carcinoma (MCF7).

2. Experimental

2.1. Synthesis

All melting points were determined on an Electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian mercury VXR-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are expressed in δ ppm units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Micro analytical Center of Cairo University.

2.1.1. Sodium (E)-(2-oxocycloalkylidine)-methanolates (2a-d)

In a three necked flask containing sodium methoxide (5.4 g, 0.01 mol), and diethyl ether (20 mL), the appropriate cyclopentanone, cyclohexanone, cycloheptanone or cyclo-octanone (0.01) mol with ethyl formate (7.5 g, 0.01 mol) was poured over it through separating funnel with efficient stirring. The solid formed was collected and used directly in the reactions [13].

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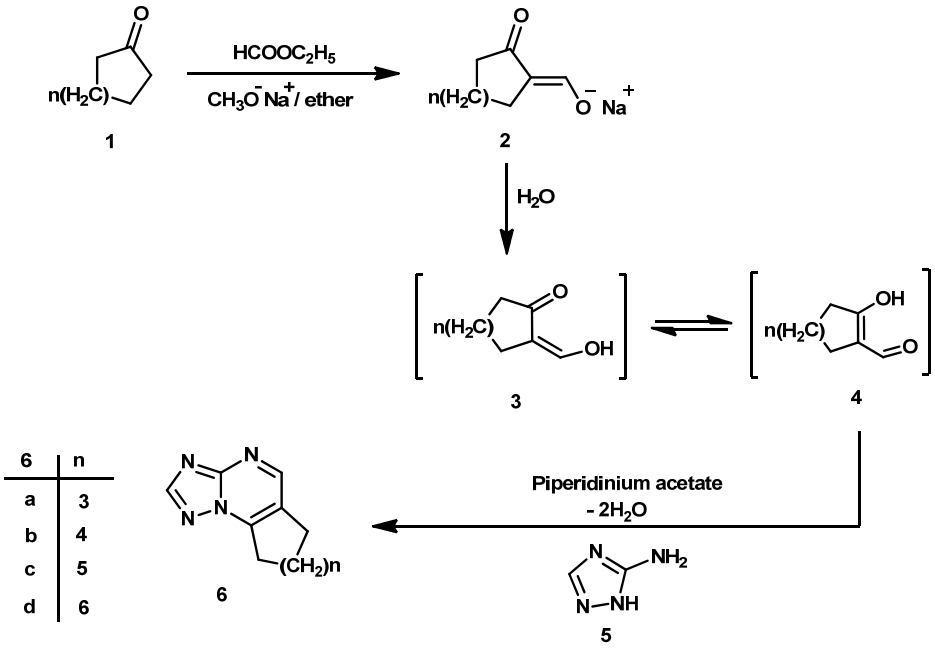

Scheme 1

2.1.2. [1,2,4]triazolo[1,5-a]pyrimidine derivatives (6a-d)

Method A: A mixture of the appropriate **2a-d** (5 mmol), 1*H*-1,2,4-triazol-5-amine **5** (0.42 g, 5 mmol) and few drops of acetic acid was thoroughly ground with pestle in an open mortar at room temperature for 3-5 min until the mixture turned into a melt. Grinding of the initial syrupy continued for 5-7 min and the progress of the reaction was monitored by TLC. The remaining solid was filtered, washed with water and recrystallized from chloroform gave the corresponding fused pyrimidines **6a-d**, respectively.

Method B: A solution of the appropriate of compound **2a-d** (5 mmol), 1*H*-1,2,4-triazol-5-amine **5** (0.42 g, 5 mmol)) and piperidinium acetate (1 mL) in H_2O (3 mL) was refluxed for 15 min. Acetic acid (1 mL) was added to the hot solution. The solid product was filtered off and recrystallized from chloroform gave product identical in all aspects (m.p. and spectra) with **6a-d** (Scheme 1).

7,8-Dihydro-6H-cyclopenta[e][1,2,4]triazolo[1,5-a] pyrimidine (**6a**): Color: Pale yellow crystals. Yield: 92%. M.p.: 154-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.25 (t, 2H, CH_2), 3.14 (d, 2H, CH_2), 3.20 (d, 2H, CH_2), 8.31 (s, 1H, pyrimidine H-4), 9.02 (s, 1H, triazole H-3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 21.55, 30.66, 30.85, 118.47, 145.33, 148.34, 154.18, 160.47. FT-IR (KBr, *ν*, cm^{-1}): 3308, 2982, 1630. MS (*m/z*, (%)): 161 (M+1, 11), 160 (M$^+$, 100), 159, (M-1, 65), 106 (12). Anal. calcd. for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.22; H, 5.31; N, 34.99%.

6,7,8,9-Tetrahydro-[1,2,4]triazolo[1,5-a]quinazoline (**6b**): Color: Pale yellow crystals. Yield: 94%. M.p.: 189-190 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.85-2.22 (m, 4H, $2CH_2$), 2.85-2.95 (m, 2H, CH_2), 3.15-3.24 (m, 2H, CH_2), 8.21 (s, 1H, pyrimidine H-4), 8.48 (s, 1H, triazole H-3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 22.65, 23.30, 23.82, 38.56, 115.25, 148.34, 154.18, 156.15, 161.28. FT-IR (KBr, *ν*, cm^{-1}): 3312, 2980, 1628. MS (*m/z*, (%)): 175 (M+1). Anal. calcd. for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 62.11; H, 5.82; N, 32.33%.

7,8,9,10-Tetrahydro-6H-cyclohepta[e][1,2,4]triazolo[1,5-a] pyrimidine (**6c**): Color: Yellow crystals. Yield: 95%. M.p.: 199-200 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.60-1.90 (m, 4H, CH_2), 2.70-2.80 (d, 1H, *J* = 6 Hz, CH_2), 2.85 (t, 2H, *J* = 6 Hz, CH_2), 3.15 (d, 1H, CH), 3.5 (t, 2H, *J* = 6 Hz, CH_2), 8.30 (d, 1H, *J* = 6Hz, pyrimidine H-4), 8.50 (d, 1H, *J* = 6 Hz, triazole H-3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 22.96, 26.52, 26.99, 28.52, 28.58, 115.16, 148.34, 154.18, 156.05, 162.08. FT-IR (KBr, *ν*, cm^{-1}): 3315, 2985, 1622. MS (*m/z*, (%)): 188 (M$^+$). Anal. calcd. for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.00; H, 6.33; N, 29.88%

6,7,8,9,10,11-Hexahydrocycloocta[e][1,2,4]triazolo[1,5-a] pyrimidine (**6d**): Color: Yellow crystals. Yield: 95%. M.p.: 219-220 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.35-150 (m, 4H, $2CH_2$), 1.80-1.90 (m, 4H, $2CH_2$), 2.92 (t, 2H, *J* = 6 Hz, CH_2), 3.45 (t, 2H, *J* = 6 Hz, CH_2), 8.50 (s, 1H, pyrimidine H-4), 8.70 (s, 1H, triazole H-3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 23.59, 26.49, 27.27, 27.59, 29.12, 30.33, 115.87, 148.34, 154.15, 156.76, 162.08. FT-IR (KBr, *ν*, cm^{-1}): 3312, 2976, 1620. MS (*m/z*, (%)):203 (M+1, 12), 202 (M$^+$, 100), 187 (35), 174 (45), 189 (35), 146 (25). Anal. calcd. for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.22; H, 6.75; N, 27.65%.

2.2. Pharmacology

2.2.1. Materials and methods

2.2.1.1. Human tumor cell lines

Human hepatocarcinoma cell lines (HepG2) and breast carcinoma cell lines (MCF7) used in this study were obtained from the American Type Culture Collection (ATCC, Minisota, U.S.A.). The tumor cell lines were maintained at the National Cancer Institute, Cairo, Egypt, by serial sub-culturing.

2.2.1.2. Preparation of the tested compounds

The two derivatives, 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4] triazolo[1,5-*a*]pyrimidine and 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine were prepared by dissolving 1:1 stock solution and stored at -20 °C in dimethyl sulfoxide (DMSO) at 100 mM. Different concentrations of the tested compounds were used 5, 12.5, 25, 50 µg/mL.

2.2.1.3. Chemicals

Dimethylsulphoxide (DMSO), RPMI-1640 medium, trypan blue, Fetal Bovine Serum, Penicillin/ Streptomycin antibiotic and Trypsin-EDTA were obtained from Sigma Aldrich Chemical Co., St. Louis, Mo, U.S.A.. *Tris*-buffer was obtained Applichem, Germany. All chemicals and reagents used in this study are of highest analytical grade.

2.2.1.4. Reagents and buffers

1. Trypan blue dye: 0.05 % of the dye was prepared and used for viability counting.
2. Fetal Bovine Serum (FBS): 10 % concentration was prepared and used for supplementation of RPMI1640 medium prior to use.
3. Penicillin/Streptomycin: 100 units/mL penicillin/2 mg/mL streptomycin were used for the supplementation of RPMI-1640 medium prior to use.
4. Trypsin-EDTA: 0.25 % solution containing 2.5 g/L Porcine trypsin and 0.38 g/L EDTA.4H_2O was used for the harvesting of cells.
5. Glacial acetic acid: 1 % was used for dissolving the unbound SRB dye.
6. Sulphorhodamine-B (SRB): 0.4 % concentration was dissolved in 1 % acetic acid was used as a protein dye.
7. Trichloroacetic acid (TCA): 50 % stock solution was prepared, 10 % solution was used for protein precipitation.
8. Tris base, 10 mM, (pH = 10.5) was used for SRB dye solubilization. It was prepared by dissolving 121.1 g of tris base in 1000 mL distilled water and pH was adjusted by 2 M HCl.

2.2.1.5. Preparation of culture medium

RPMI-1640 medium was used for culturing and maintenance of the human tumor cell lines. The medium was supplied in a powder form. The working solution was prepared by dissolving 10.4 g powder and 2 g sodium bicarbonate dissolved in 1 L distilled water. The medium was then sterilized by filtration in a Millipore bacterial filter (0.22 µm). The prepared medium was kept in a refrigerator (4 °C). Before use, the medium was warmed at 37 °C in a water bath and the supplemented with 1% penicillin/(2 mg/mL) streptomycin and 10% fetal bovine serum.

2.2.2. Procedures

2.2.2.1. Maintenance of the human cancer cell lines in the laboratory

A cryotube containing frozen cells was taken out of the liquid nitrogen container and then thawed in a water bath at 37 °C. The cryotube was opened under strict aseptic conditions and its contents were supplied by 5 mL supplemented medium drop by drop in a 50 mL sterile falcon tubes. The tube was incubated for 2 hours then centrifuged at 1200 rpm for 10 min and the supernatant was discarded. The supernatant was discarded and the cell pellet was suspended and seeded in 5 mL supplemented medium in T25 Nunclon sterile tissue culture flasks. The cell suspension was incubated and followed up daily the supplemented medium was replaced every 2-3 days. Incubation was continued until a confluent growth was achieved and the cells were freshly sub cultured before each experiment to be in the exponential phase of growth.

2.2.2.2. Collection of cells by trypsinization

The medium was discarded. The monolayer cell was washed twice with 5 ml phosphate buffered saline. All the adherent cells were dispersed from their monolayer by the addition of 1 mL trypsin solution (0.25 % trypsin, *w*:*v*) for 2 minutes.

2.2.2.3. Determination and counting of viable cells

50 µL of 0.05 % trypan blue solution was added to 50 µL of the single cell suspension. The cells were examined under the inverted microscope using the haemocytometer. Non stained (viable) cells were counted and the following equation was used to calculate the cell count/mL of cell suspension.

$$\text{Viable cells/mL} = \text{number of cells in 4 quarters} \times 2 \text{ (dilution factor)} \times 10^4 / 4 \quad (1)$$

The cells were then diluted to give the required cell number for each experiment.

2.2.2.4. Cryopreservation of cells

To avoid the loss of the cell line, excess cells were preserved in liquid nitrogen. Equal parts of the cell suspension and freezing medium (10 % DMSO in supplemented medium) were dispersed to cryotubes. The cryotubes were racked in appropriately labeled polystyrene boxes, gradually cooled till reaching -80 °C. Then the cryotubes were stored in liquid nitrogen (-180 °C) till use.

2.3. Determination of potential cytotoxicity of drug on human cancer cell line

The cytotoxicity was carried out using sulphorhodamine-B (SRB) assay following the method reported by Vichai and Kirtikara [13] and Hussein and Ahmed [14,15]. SRB is a bright pink aminoxanthrene dye with two sulphonic groups. It is a protein stain that binds to the amino groups of intracellular proteins under mildly acidic conditions to provide a sensitive index of cellular protein content.

Cells were maintained in RPMI-1640 medium with 10% foetal calf serum, sodium pyruvate, 100 U/mL penicillin and 2 mg/mL streptomycin at 37 °C and 5% CO_2. Cells were seeded in 96-well micro titer plates at initial concentration of 3×10^3 cell/well in a 150 µL fresh medium and left for 24 hours to attach to the plates. Different concentrations 0, 5, 12.5, 25, and 50 µg/mL of the tested compounds were added. For each concentration, 3 wells were used. The plates were incubated for 48 hours. The cells were fixed with 50 µL cold trichloroacetic acid 10% final concentration for 1 hour at 4 °C. The plates were washed with distilled water using (automatic washer Tecan, Germany) and stained with 50 µL 0.4 % SRB dissolved in 1 % acetic acid for 30 minutes at room temperature. The plates were washed with 1 % acetic acid and air-dried. The dye was solubilized with 100 µL/well of 10 M tris base (pH = 10.5) and optical density (O.D.) of each well was measured spectrophotometrically at 570 nm with an ELISA micro plate reader (Sunrise Tecan reader, Germany). The mean background absorbencies were automatically subtracted and mean values of each drug concentration was calculated. The experiment was repeated 3 times. The percentage of cell survival was calculated using the formula, surviving fraction = O.D. (treated cells)/O.D. (control cells). The IC_{50} values (the concentrations of the compound required to produce 50% inhibition of cell growth) were also calculated.

3. Results and discussion

3.1. Synthesis

Treatment of 1*H*-1,2,4-triazol-5-amine (**5**) with sodium (*E*)-(2-oxocyclooctylidene)methanolate (**2d**) in acetic acid containing piperidinium acetate afforded a product namely

6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4]triazolo[1,5-*a*] pyrimidine (**9d**) (Scheme 1). The structure was confirmed by elemental analysis, spectral data and X-ray single crystal diffraction data (Figure 1) (Table 1 and 2). The reaction seemed to be *via* the initial nucleophilic attack by the exocyclic amino group at the formyl group **4**, which formed *in situ* from compound **2d** with water, followed by cyclization and elimination of one molecule of water leading to the formation of the product **6d** (Scheme 1).

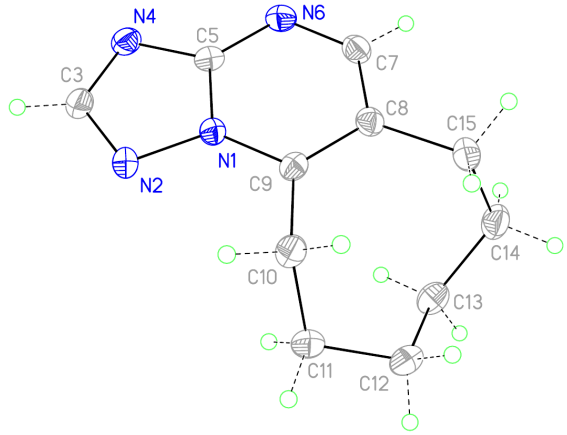

Figure 1. Crystal structure of compound **6d**.

Table 1. Crystal data and structure refinement for compound **6d**.

Empirical formula	$C_{11}H_{14}N_4$
Formula weight	202.12
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 7.3161(15) Å
	b = 10.324(2) Å
	c = 13.745(3) Å
	α = 90 °
	β = 105.13(3) °
	γ = 90 °
Volume	1002.2(4) Å^3
Z	4
Density (calculated)	1.288 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	428
Crystal size	0.12 × 0.09 × 0.04 mm^3
Theta range for data collection	2.50 to 24.72 °.
Index ranges	$-7 \le h \le 8$, $-12 \le k \le 12$, $-16 \le l \le 15$
Reflections collected	15083
Independent reflections	1662 [R(int) = 0.0275]
Completeness to theta = 24.72 °	97.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1662 / 0 / 136
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0424, wR2 = 0.1182
R indices (all data)	R1 = 0.0441, wR2 = 0.1196
Largest diff. peak and hole	0.187 and -0.730 e.Å^{-3}

Similarly, treatment of compound **5**, were reacted with the appropriate sodium (2-oxocyclopentylidene)methanolate (**2a**), sodium (2-oxocyclohexylidene)methanolate (**2b**) or sodium (2-oxocycloheptylidene)methanolate (**2c**), afforded 7,8-dihydro-6H-cyclopenta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (**6a**), 6,7,8,9-tetrahydro-[1,2,4]triazolo[1,5-*a*]quinazoline (**6b**) and 7,8,9,10-tetrahydro-6*H*-cyclohepta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine (**6c**), respectively.

3.2. Cytotoxicity against different human cancer cell lines in vitro

Many triazolopyrimidine derivatives were previously reported to have anti-tumour effects [17]. Navarro [1] found that 4,7-*H*-5-methyl-7-oxo[1,2,4]triazolo[1,5-*a*]pyrimidine have a moderate antitumor activity against breast carcinoma, MCF7 cell lines.

Table 2. Bond lengths [Å] and angles [°] for compound **6d**.

Atom-Atom	*Bond lengths*
N1-N2	1.363(2)
N1-C9	1.370(2)
N1-C5	1.386(2)
N6-C7	1.317(2)
N6-C5	1.339(2)
C8-C9	1.374(2)
C8-C7	1.412(2)
C8-C15	1.506(2)
C9-C10	1.493(2)
C5-N4	1.339(2)
C10-C11	1.539(2)
C3-N2	1.328(2)
C3-N4	1.343(2)
C15-C14	1.536(3)
C12-C11	1.533(2)
C12-C13	1.536(2)
C13-C14	1.529(3)
N2-N1-C9	127.20(14)
N2-N1-C5	109.39(13)
C9-N1-C5	123.38(14)
Atom-Atom-Atom	***Bond angles***
C7-N6-C5	115.35(14)
C9-C8-C7	118.53(15)
C9-C8-C15	121.03(15)
C7-C8-C15	120.42(15)
N1-C9-C8	115.17(15)
N1-C9-C10	118.18(14)
C8-C9-C10	126.63(15)
N6-C5-N4	129.02(15)
N6-C5-N1	121.69(15)
N4-C5-N1	109.28(14)
C9-C10-C11	114.83(14)
N2-C3-N4	117.32(15)
C5-N4-C3	102.39(13)
C3-N2-N1	101.61(14)
N6-C7-C8	125.85(16)
C8-C15-C14	112.66(14)
C11-C12-C13	115.56(14)
C12-C11-C10	116.35(14)
C14-C13-C12	116.17(15)
C13-C14-C15	115.38(14)

For evaluation of anti-tumor cytotoxicity of the synthesized compounds 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4] triazolo [1,5-*a*]pyrimidine and 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4] triazolo[1,5-*a*]pyrimidine, two different human cancer cell lines were used: HepG2 (liver carcinoma cell line) and MCF7 (breast carcinoma cell line).

The two tested 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4] triazolo[1,5-*a*]pyrimidine and 7,8-dihydro-6*H*-cyclopenta[*e*] [1,2,4]triazolo[1,5-*a*]pyrimidine produced a profound cytotoxic effects against human hepatocarcinoma cell lines (HepG2). The survival fraction was decreased in a dose dependent manner as the dose was increased from 5 to 50 µg/mL. The IC_{50} of 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4]triazolo[1,5-*a*] pyrimidine and 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine against HepG2 was 12.13 µg/mL and 14.75 µg/mL, respectively (Figure 2 and 3).

Similar to the effect on HepG2, the two tested triazolopyrimidine derivatives had potential cytotoxic effects on breast carcinoma cell lines (MCF7). The survival fraction was gradually and sharply decreased as the concentration of the tested derivatives was increased from 5 to 25 µg/mL. As the concentration in the culture media was increased from 25 to 50 µg/mL, the cytotoxic effects were more or less not progressed. The IC_{50} of 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4]triazolo [1,5-*a*]pyrimidine and 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4] triazolo[1,5-*a*]pyrimidine against MCF7 was 14.25 µg/mL and 13.50 µg/mL, respectively (Figure 4 and 5).

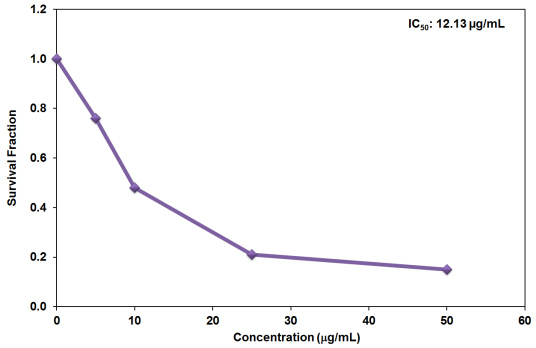

Figure 2. Antiproliferative effect of 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine on HepG2 carcinoma cell lines.

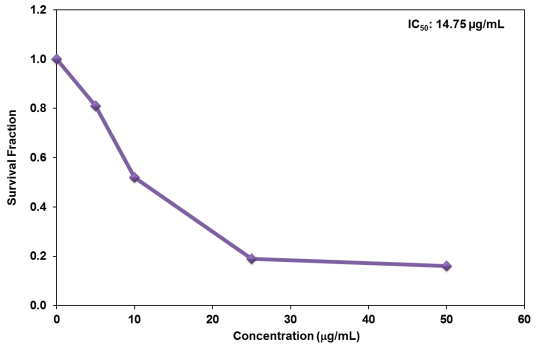

Figure 3. Antiproliferative effect of 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine on HepG2 carcinoma cell lines.

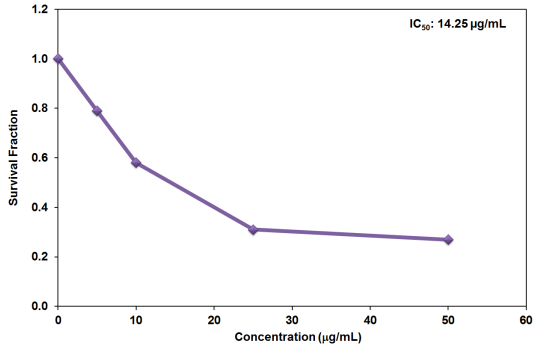

Figure 4. Antiproliferative effect of 6,7,8,9,10,11-hexahydrocycloocta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine on MCF7 carcinoma cell lines.

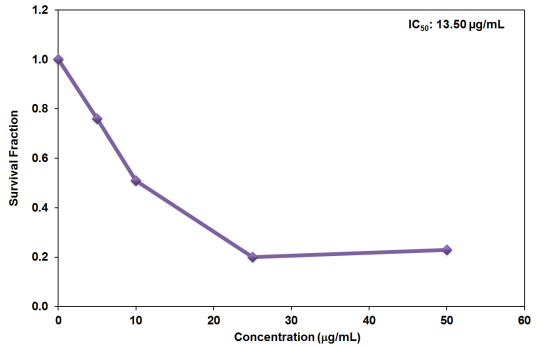

Figure 5. Antiproliferative effect of 7,8-dihydro-6*H*-cyclopenta[*e*][1,2,4]triazolo[1,5-*a*]pyrimidine on MCF7 carcinoma cell lines.

4. Conclusion

Synthesis of new [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives was accomplished and structures were elucidated by means of various characterization techniques such as elemental analyses, spectral (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR), and X-ray single crystal diffraction data. These derivatives were evaluate for in vitro anti-tumor using various human cancer cell lines

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